EAST Search History

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L2	21	(delete or deleted or dplete or depleted or deficient) with myeloid with ((t adj cell) or (t-cell))	US-PGPUB; USPAT; EPO; DERWENT	OR	OFF	2006/08/07 09:16
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L5	21	(delete or deleted or deplete or depleted or deficient) with myeloid with ((t adj cell) or (t-cell))	US-PGPUB; USPAT; EPO; DERWENT	OR	OFF	2006/08/07 09:18

(28) The preferred source of hematopoietic cells from mammal M2 is bone marrow, either untreated or depleted of T cells. Other suitable sources of hematopoietic cells which may also be used include, for example, **spleen** cells, fetal liver cells or peripheral blood cells, which may be cultured or non-cultured, along with supporting stromal cells. Thus, the hematopoietic cells transplanted from mammal M2 may be selected or derived from at least one of:

(29) (i) unfractionated or fractionated bone marrow cells;

(30) (ii) unfractionated or fractionated blood cells;

(31) (iii) unfractionated or fractionated **spleen** or thymus cells;

(32) (iv) unfractionated or fractionated cord blood cells;

(33) (v) unfractionated or fractionated fetal cells (liver, thymus, bone marrow, **spleen** or blood); and

(34) (vi) any combination thereof.

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(45) Unfractionated or fractionated bone marrow cells may include, e.g., **T cell-depleted,** or different cell populations of the **myeloid,** erythroid, megakaryocytoid or lymphoid lineages and their precursors and/or combinations thereof. Unfractionated or fractionated blood cells may include, e.g., subpopulations of different lymphocytes, macrophages, monocytes, platelets or erythrocytes and their precursors and/or combinations thereof. Preferably, fractionated blood cells are used which are human peripheral blood leukocytes (PBL). Pluripotent stem cells and/or other hematopoietic progenitors derived from B cell-depleted and T cell-depleted peripheral blood leukocytes may also be included.

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United States Patent [19]

Reisner

[11] Patent Number: 5,709,843

[45] Date of Patent: Jan. 20, 1998

[54] **ENGRAFTMENT AND DEVELOPMENT OF XENOGENEIC CELLS IN NORMAL MAMMALS HAVING RECONSTITUTED HEMATOPOIETIC DEFICIENT IMMUNE SYSTEMS**

[75] Inventor: **Yair Reisner**, Tel Aviv, Israel

[73] Assignee: **Yeda Research and Development Co. Ltd.**, Rehovot, Israel

[21] Appl. No.: **347,088**

[22] Filed: **Nov. 23, 1994**

Related U.S. Application Data

[60] Division of Ser. No. 61,706, May 17, 1993, which is a continuation-in-part of Ser. No. 892,911, Jun. 3, 1992, abandoned, and Ser. No. 792,480, Nov. 15, 1991, abandoned, said Ser. No. 892,911, is a continuation-in-part of Ser. No. 792,480, which is a continuation-in-part of Ser. No. 618,303, Nov. 26, 1990, abandoned.

[30] **Foreign Application Priority Data**

Jan. 15, 1990 [IL] Israel 93067
Jun. 4, 1991 [IL] Israel 98 369

[51] **Int. Cl.**[6] **A61K 49/00**; G01N 31/00; A01N 63/00; A01N 65/00

[52] **U.S. Cl.** **424/9.2**; 424/9.1; 424/93.1; 424/93.3; 424/93.7; 424/93.71; 424/520; 435/4; 435/5; 800/2

[58] **Field of Search** 800/2; 424/9.2, 424/9.1, 93.1, 93.3, 93.7, 93.71, 520; 435/5, 4

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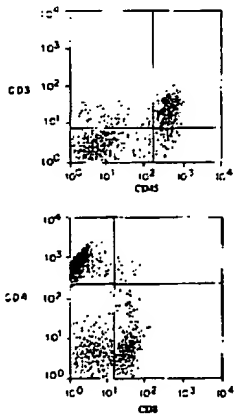
[57] **ABSTRACT**

Non-human chimeric mammals are created from a mammal having hematopoietic cells replaced with hematopoietic cells from a hematopoietic deficient mammal donor, and optionally in which xenogeneic cells and/or tissue are engrafted. The xenogeneic, preferably human, cells or tissue may be hematopoietic cells, in which case the chimeric mammal can produce xenogeneic B and/or T cells, and can be used as a source of mammalian, preferably human, monoclonal antibodies and/or T cells. Alternatively, the xenogeneic cells or tissue may be non-hematopoietic, such as normal or pathological cells or tissue, which can form a stable transplant in the chimeric mammal and thus can be used as an animal model of various pathologies or to test therapeutic or diagnostic agents or modalities.

23 Claims, 13 Drawing Sheets



transplantation of SCID bone marrow (1×10^6 cells) (Day 1). Takes of grafted human tissue are evaluated by histology and/or by immunohistochemistry. Immunohistological tests of thymus implants suggest that, within an observation period of one month after transplantation, the stroma structure of human thymus implants was accepted and maintained under the kidney capsules of the BALB/c or BNX mice.

Vascularised human liver (not shown) has lost its typical architecture, but human hepatocytes and other components, such as bile ducts and Kupfer cells, could be identified by histological examination.

EXAMPLE XIII

Lack of GVHD in Chimeric Mice According to the Present Invention Without Use of Immunosuppressive Agents.

In a model according to the present invention, administration of IL-2 is not needed or used in order to avoid GVHD (graft-versus-host disease) completely. In contrast to the autologous bone marrow in Sachs' model, the SCID bone marrow which is used for radioprotection cannot produce T or B lymphocytes, due to its inherent deficiency. Thus, the present invention avoids the problem of host-versus-graft reaction not by active specific tolerance induction but rather by inducing a permanent state of hematopoietic deficiency. By the method of the present invention, a marked lymphoid chimerism following transplantation of T cell depleted allogeneic bone marrow or human bone marrow together with the SCID bone marrow. To illustrate this difference, in lethally irradiated BALB/c mice, the chimerism obtained after transplantation of T cell depleted C3H ($H\text{-}2^k$) bone marrow plus T cell depleted SCID ($H\text{-}2^d$) bone marrow to T cell depleted C3H bone marrow plus T cell depleted autologous bone marrow (BALB/c) ($H\text{-}2^d$). As can be seen in FIG. 11, when the allogeneic bone marrow depleted of T cells are transplanted with SCID bone marrow, a marked lymphoid engraftment of the allogeneic cells is found without GVHD, whereas if the Sachs' approach is tested and we transplant T cell depleted autologous bone marrow (instead of the SCID bone marrow) together with the same T cell depleted allogeneic bone marrow, the latter cells do not engraft. Moreover, as shown below, the SCID bone marrow can be taken from an H-2 mismatched donor, as opposed to the Sachs' model, which necessitates the use of autologous bone marrow. Thus, the two models are based on fundamentally different principles and lead to entirely distinct mice.

It has been shown that several mouse and human cytokines are not cross reactive between the species, at least not with the same efficiency. Therefore, any extrapolation from an allogeneic transplantation mouse model or even from a rat to mouse transplantation model, to the transplantation of human bone marrow in mice is not obvious. Moreover, primary antibody responses are extremely inefficient in allogeneic mouse models of bone marrow transplantation. The achievement of the present invention in obtaining primary human anti-DNP response in some human/mouse chimera could not be considered obvious on the basis of our relevant murine model and clearly not by the irrelevant Sachs' model. Even if the Sachs' model was based on a similar principle to our model, the engraftment of human cells in lethally irradiated mice and their ability to induce human antibodies against DNP-KLH could not be anticipated by extrapolation from any existing murine model.

EXAMPLE XIV

Lack of Need for M2 H-2 Compatible Hematopoietic Cells With Mammal M1

(i) Studies in the allogeneic murine model verified that the recipient strains need not be BALB/c and we were able to achieve long-term engraftment of T cell depleted BALB/c bone marrow in lethally irradiated C3H recipients when the transplant was administered together with bone marrow from CB17 SCID ($H\text{-}2^d$) mouse.

(ii) SCID bone marrow ($H\text{-}2^d$) need not be H-2 compatible with the recipient mouse. Thus, transplantation of human PBL into lethally irradiated C57BL/6 nude mice ($H\text{-}2^b$) was engrafted when administered one day after transplantation of T cell depleted SCID bone marrow ($H\text{-}2^d$). Likewise, lethally irradiated BNX mice (outbred) transplanted with SCID bone marrow were engrafted successfully with human PBL (as documented by double staining of the chimeric PBL or spleen cells with anti-Leu4 and anti-CD45).

(iii) Moreover, as shown in Example IX, even rats could be engrafted simultaneously with mouse SCID bone marrow (which generated red blood cells) and with human PBL.

All references cited herein, including journal articles or abstracts, published or corresponding U.S. or foreign patent applications, issued U.S. or foreign patents, or any other references, are entirely incorporated by reference herein, including all data, tables, figures, and text presented in the cited references. Additionally, the entire contents of the references cited within the references cited herein are also entirely incorporated by reference.

Reference to known method steps, conventional methods steps, known methods or conventional methods is not in any way an admission that any aspect, description or embodiment of the present invention is disclosed, taught or suggested in the relevant art.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art (including the contents of the references cited herein), readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance presented herein, in combination with the knowledge of one of ordinary skill in the art.

What is claimed is:

1. A method for evaluating the efficacy of a therapeutic agent or modality potentially useful for treating a human disease, comprising:

(a) providing a chimeric mouse or rat M4 having xenogeneic cells or xenogeneic tissue, said mouse or rat M4 comprising a mouse or rat M1, other than a SCID mouse the hematopoietic cells of which have been substantially destroyed, said mouse or rat M1 having transplanted therein cells or tissue from at least two different sources, at least one of said sources being hematopoietic cells from a mouse M2 having a T and/or B cell immunodeficiency, and at least a second of said sources being human cells or tissue which are either

(i) pathological or diseased cells or tissue, or

(ii) normal cells or tissue susceptible to being infected by a pathogen causing the human disease, wherein said T and/or B cell immunodeficiency of said mouse M2 is such that the T and/or B cell immunodeficiency can be reconstituted with xenogeneic hematopoietic cells,

(b) when said cells or tissue are said normal cells or tissue, infecting said mouse or rat M4 with a pathogen;

(c) treating said mouse or rat M4 with the therapeutic agent or modality; and

(d) testing said mouse or rat M4 for signs of said disease or for symptoms associated with said disease, the efficacy of said agent or modality being inversely related to the extent of said signs or symptoms.

2. A method according to claim 1 wherein said disease is AIDS and said pathogen is an HIV.

3. A method according to claim 1, wherein said disease is hepatitis and said pathogen is a human hepatitis virus.

4. A method according to claim 3, wherein said hepatitis virus is a hepatitis C virus.

5. A method according to claim 1, wherein said pathogen is a virus or toxin.

6. A method in accordance with claim 1, wherein said chimeric mouse or rat M4 is one in which said human cells or tissue are normal human cells or tissue susceptible to being infected by a pathogen causing the human disease.

7. A method according to claim 6, wherein said disease is AIDS and said pathogen is an HIV.

8. A method according to claim 6, wherein said pathological human cells are hepatitis C virus infected cells.

9. A method according to claim 6, wherein said pathogen is a virus or toxin.

10. A method in accordance with claim 1, wherein said chimeric mouse or rat M4 is one in which said human cells or tissue are pathological or diseased cells or tissue.

11. A method according to claim 10, wherein said pathological or diseased cells or tissue is selected from the group consisting of an autoimmune cell, a cancer cell, a pathological blood cell, a human T cell, a lymphokine-activated killer cell, a cytotoxic T lymphocyte, a human T cell derived cell and a human B cell derived cell.

12. A method according to claim 1, wherein said chimeric mouse or rat M4 is one in which said human cells or tissue are pathological cells or tissue.

13. A method according to claim 12, wherein said pathological human cells or tissue are malignant cells or tissue selected from the group consisting of solid tumor cells or tissue and leukemia cells or tissue.

14. A method according to claim 12, wherein said mammal M1 is a mouse, said mammal M2 is a mouse, and said pathological human cells or tissue are cells or tissue of cancer samples selected from the group consisting of colon cancer, breast cancer, ovary cancer, pancreas cancer, lung cancer, stomach cancer, kidney cancer, prostate cancer, melanoma, neuroblastoma, glioblastoma, myeloid leukemia, lymphatic leukemia, and monocytic leukemia.

15. A method according to claim 14, wherein said human pathological cells or tissue are melanoma cells or melanoma tissue.

16. A method in accordance with claim 12 for chemotherapy sensitivity testing of a drug against a human solid tumor, wherein said chimeric mouse or rat M4 is one in which said pathological human cells or tissue are human solid tumor cells or tissue and said testing step comprises evaluating the effect of said chemotherapy on said solid tumor cells or tissue.

17. A method according to claim 16, for testing the chemotherapy activity of a drug against the tumor tissue of an individual patient, wherein said chimeric mouse or rat M4 is one in which said human solid tumor cells or tissue originate from the tumor of said individual.

18. A method in accordance with claim 12 for chemotherapy sensitivity testing of a drug against leukemia, wherein said chimeric mouse or rat M4 is one in which said pathological human cells or tissue are human leukemia cells and said testing step comprises evaluating the effect of said chemotherapy on said leukemia cells.

19. A method according to claim 18 for testing the chemotherapy activity of a drug against the leukemia cells of an individual patient, wherein said chimeric mouse or rat M4 is one in which said human leukemia cells originate from leukemia cells of said individual.

20. A method in accordance with claim 12, wherein said chimeric mouse or rat M4 is one in which said human cells or tissue are malignant cells or tissue.

21. A method according to claim 20, wherein said malignant cells or tissue are obtained by a biopsy from a human cancer patient.

22. A method in accordance with claim 20, wherein said testing step comprises evaluating the effect of said therapeutic agent or modality on said malignant cells or tissue.

23. A method in accordance with claim 1, wherein said testing step comprises testing for the presence or amount of said pathogen or of an antigen of said pathogen in a body fluid or tissue of the treated chimeric mouse or rat M4.

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Child Data

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Inventor Information for 09/830176

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Last Name = RON
First Name = YACOV

Application#	Patent#	Status	Date Filed	Title	Inventor Name
08100546	Not Issued	166	07/30/1993	EFFICIENT GENE TRANSFER INTO PRIMARY MURINE LYMPHOCYTES OBVIATING THE NEED FOR DRUG SELECTION	RON, YACOV
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